ENCEPHALITIS

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Introduction
A patient with acute encephalitis poses the greatest challenge for the consulting neurologist. Establishing an etiological diagnosis early in the course of the illness can alter the course of the illness hence early diagnosis is critical. Initial investigations should attempt to determine if the cause is infectious, autoimmune or toxic as the approach to treatment is different for each. Unfortunately, for many cases of encephalitis the diagnosis remains obscure and for some viral encephalitides no anti-viral therapy is available. However, proper supportive therapy can make a major difference to the ultimate outcome, and the withdrawal of any offending immunosuppressive agents that may be beneficial for non-infectious causes of encephalitis can be critical for survival.

The differential diagnosis of a patient with acute encephalitis should include, infectious, parainfectious autoimmune and toxic or metabolic encephalopathy. A careful history of exposure to toxins, medications and relevant laboratory testing can guide one to investigate and treat a toxic encephalopathy. If there is accompanying meningitis, bacterial infections should be a top consideration and treated aggressively even if the CSF results are not yet available. NMDA receptor and autoimmune limbic encephalitis can be determined by antibody testing in blood and CSF. Of all infectious causes of encephalitis, the viral encephalitidies are probably the most challenging to diagnose. Hence this talk is focused on how to diagnose a patient with viral encephalitis and how to investigate a patient with an unknown cause encephalitis. Excellent reviews are available of many of the viral causes of encephalitis which are listed below. For the purpose of this syllabus, we have summarized the key features that a busy neurologist should know and can use this material as a guide for their practice when faced with such a patient.

Herpes encephalitis:
HSV-1: Most of you are quite familiar with the clinical presentations of herpes encephalitis due to HSV-1. Hence I have focused this discussion on the major pitfalls. This is the only form of viral encephalitis that is treatable. Antiviral drugs can change the course of the illness. Hence earlier they are initiated the better the outcome. However, the patients often have a rather acute onset of symptoms and are seen in the emergency room and may thus be mistaken for a stroke. Since the infection involves the temporal lobes initially, they may present with seizures, altered conciousness or aphasia or memory dysfunction. Motor symptoms only arise once the frontal lobes are involved. A CT scan done in the ER may show a hypodense lesion and they may get admitted to the stroke unit. The diagnosis is often not considered until a day or two later when the symptoms are progressing. Fever is almost always present and this should be a clue to the diagnosis. Headache is also not uncommon. Even though the virus resides in the trigeminal ganglia and is thought to infect the temporal lobes in proximity to the ganglia, there are no accompanying oral lesions. Acyclovir can be initiated even if the CSF results are not yet back. The drug is well tolerated with few side effects. Hence it is better to be safe than sorry. A delayed or missed diagnosis can frequently end in death or severe morbidity for the patient who otherwise has a significant chance of recovery when treated preemptively.

HSV-2 can also cause a recurrent meningoencephalitis.These patients often have a past history of genital herpes. Meningitis is more prominent in these patients.

HHV-6: In immunocompromised patients, often on cancer chemotherapy, organ transplants, children or the elderly, HHV-6 can cause an encephalitis and usually involves the mesial temporal lobe. Hence the clinical manifestations may overlap with those of HSV-1 encephalitis. A challenge with diagnosis of HHV-6 encephalitis is that this virus can get activated in a variety of inflammatory conditions and about 1% of the population has HHV-6 integrated in their chromosome. Hence if the lab gives you a very high value of detection of HHV-6, you might want to ask if the virus could be coming from chromosomal DNA.

CMV is another herpes virus that can cause an acute encephalitis in severely immunocompromised individuals. Clinically it may be hard to distinguish it from other causes of acute encephalitis. But an astute clinician will always look at the retina with an ophthalmoscope and it there is presence of retinitis with areas of pale infarcts and hemorrhages, and can make the diagnosis at the bedside. The only other virus that can cause a similar retinitis is VZV, but within the CNS VZV encephalitis often presented with stroke like episodes. On MRI, classically CMV encephalitis causes enhancing lesions lining the ventricles, but the virus may invade the parenchyma as well. One other unique aspect of CMV encephalitis is the possibility that the MRI may appear normal, so in a patient with advanced immunosuppression and an MRI that appears normal at least on initial review, CMV encephalitis should be considered high on the differential.

EBV is a rare cause of encephalitis. In patients with advanced immunosuppression, EBV should be considered in CSF testing, however false positive results may be common in because of the high prevalence of asymptomatic EBV infection and the tendency for EBV reactivation during other central nervous system diseases. The microbiology lab reporting a positive EBV PCR result in CSF should be able to tell you the cycle threshold number to help decide whether the result is pathologic or, when more indicative of low-level CSF virus, an indication of non-specific reactivation.

Establishing the etiology of these viral encephalitides is important since they will respond to antiviral drugs and the choice of the drug and the dose will depend on the virus identified.

Arbovirus encephalitides
Arbovirus is a portmanteau of the words "arthropod borne" hence they are viruses transmitted by mosquitos, ticks, fleas and other arthropods.

Tick borne encephalitis/ Powassan virus
Tick-borne encephalitides are a rare cause of viral encephalitis in Europe and the US. In Europe, the tick is primarily *Ixodes ricinus* and the disease is referred to as Tick borne encephalitis but in North America there are more varied species that include *Ixodes scapularis* (deer tick in Northeast US) and *Ixodes cookei* (woodchucks and rodents; Great lakes region), which also transmits Lyme's disease. In North America, it is also termed Powassan virus encephalitis. Within the last year, there have been several cases in the region that spans the New England area to Virginia. There are two lineages of the Powassan virus. Mean incubation period is 8 days (4-28 days) after the tick bite. Patients present with a flu like illness for a week followed by a symptom free interval and then the neurological symptoms emerge with fever and altered consciousness or seizures. The clinical spectrum can range from a mild meningitis to severe encephalitis with or without radiculits and myelitis. Patients with Powassan encephalitis may have a mild macular rash on the trunk and may have vomiting or diarrhea and focal neurological symptoms may be present at onset. Rarely mild thrombocytopenia may occur. CSF pleocytosis is common with up to 1000 cells/ul and with lymphocytic or polymorphic predominance. MRI lesions involves the deep gray matter including the thalami (most common), striatum, midbrain nuclei, and cerebellar nuclei. These lesions typically do not enhance, except for some leptomeningeal enhancement. If myelitis occurs, it involves the anterior horn cells, typically lower thoracic and lumbar cord. Contrary to brain lesions, these tend to enhance and may have surrounding meningeal enhancement. Rarely posterior horn cells are involved.

Mosquito borne encephalitides.
While West Nile virus and Zika have made the news recently, there are several viruses that fall into this category. Japanese B encephalitis virus, Dengue, Chikungunya virus and yellow fever can all cause acute encephalitis and their genetic makeup is closely related with a likely common ancestor. Although currently there is not effective antiviral compound for treating these infections, terrific strides are being made to develop drugs against Zika virus infection. If is quite likely that many of these drugs will also be effective in treating the other related viruses, hence it is important to develop a good understanding of each of these infections. Importantly, these viruses often have a prodrome of a flu like illness and then is followed by the neurological manifestations, hence a careful history is

key. One feature that distinguishes Zika from the others is that it often results in conjunctivitis during the prodromal phase while the others do not. A rash is more common than fever in the prodromal stage of Zika infection, as well. With regards to Dengue encephalitis, hemorrhages are common for example there may be mucosal bleeding with low platelets. In some patients, gastrointestinal symptoms may be prominent. There are four different serotypes of the virus. Interestingly, infection with any one of them alone usually produces mild symptoms, but when infected with a second serotype the infection produces severe symptoms. This suggests that the immune response from the first infection does not protect against the other serotypes but rather, it leads to an enhanced virulence.

Several other arboviruses, such as the equine encephalitis virus and St. Louis encephalitis cause rare outbreaks. Testing for these viruses is not available in commercial laboratories. State health departments or the CDC have the ability to do the viral and serological assays and hence need to be contacted in such cases.

CNS Immune reconstitution syndrome with HIV infection:
This syndrome may present as an acute encephalitis since the presenting signs may be a focal or generalized seizure. These patients are usually well controlled on antiretroviral drugs (ART). Important clues are, that they have a low CD4 cell count and very high plasma HIV viral load at the time of initiation of ART and have been on the drugs for only a few weeks or months, or there has been a change in their ART within the same time range. Spinal fluid shows presence of virus while it may be undetectable in the blood at the time of neurologic symptom onset. MRI of the brain may show diffuse white matter changes and can be initially mistaken for PML. Proper recognition of this syndrome is necessary, since it can be treated by a course of corticosteroids to counterbalance the overwhelming immune activation associated with the initial stages of antiretroviral therapy.

Enteroviral encephalitis:
Most enteroviruses cause an acute flaccid myelitis because they affect the anterior horn cells of the spinal cord. However, some enteroviruses such as enterovirus-71, echovirus and coxsackie virus can cause a meningoencephalitis. Usually the encephalitis is mild and there is good recovery except in neonates where it may be severe.

Undiagnosed encephalitis:
Even if the patient has classical symptoms of encephalitis, the underlying cause may not be apparent until days after the presentation and in some cases never be found. Below is an outline on how best to collect specimens early in the course of the illness, In these patients, empirical therapy may be tried. If fever is present, and bacterial meninigitis has been ruled out, treatment with acyclovir should be initiated immediately and then continued with the relevant investigations.

<u>Laboratory testing</u>.
Viral PCR assays: Most medical centers in developed countries are able to perform a viral PCR for a small number of viruses. These include HSV-1, VZV, CMV, EBV and JCV. These are all DNA viruses and are very stable in biological fluids hence can be easily detected. However, early in the course of the illness these tests may be negative. They are often reported as being either positive or negative. It is useful to ask you laboratory what the detection cut off limit might be. Most often the cut off values are about 200-500 copies per ml. In our experience, we have found that in early cases of PML, when JCV is negative in the CSF from other laboratories, research labs at our institution can still detect it since they can go to a sensitivity of 10 copies/ml.

Great difficulty arises in trying to diagnose encephalitis due to RNA viruses. RNA is easily degraded and only small amounts may spill out into the CSF unless there is an accompanying meningitis. Hence proper specimen collection is key. If possible keep the CSF in the tubes on ice and transport to the microbiology lab. At least one ml of fluid is needed for extraction of RNA and DNA. Some viruses are cell associated, hence the lab may be instructed to extract the nucleotides from the cell free fluid and the cell pellet separately especially if pleocytosis is present.

<u>Specimen Collection</u>:
As neurologists we always think that the diagnosis of any neurological condition can best be made by evaluation of the CSF. While this may be the case for some, others such as enteroviruses may be released in the stool for days and weeks after it can no longer be detected in the CSF. Hence it is critically important to collect a wide range of biological samples early at the time of presentation. This should include nasopharyngeal swabs, saliva,

broncheal secretions if any, urine, fecal material and skin biopsy if a rash or ulceration is present. Blood specimens should include serum for antibody testing and plasma and leukocytes for viral PCR or culture.

Consultations:
Wide-ranging consultations may be critically important for rare or difficult-to-detect cases. Ophthalmology and dermatology services often provide specialized examinations that might reveal pathogen-specific abnormalities. Additionally, a systemic workup for associated conditions, for example adrenal pathology often coincides with CMV encephalitis, can often be helpful.

Recommended Reading

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